Safety and Efficacy of Radioembolization in Elderly (≥ 70 Years) and Younger Patients With Unresectable Liver-Dominant Colorectal Cancer

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Abstract

Patients with liver-dominant metastatic colorectal cancer (mCRC) benefit from increased control of the hepatic disease. Radioembolization (RE) can provide significant hepatic tumor control in eligible patients, but advanced age is a factor of unclear importance. Fortunately, results from an 11-center experience demonstrate similar safety and efficacy with RE in patients < 70 years of age and patients ≥ 70 years of age.

Background: The effects of advancing age on clinical outcomes after radioembolization (RE) in patients with unresectable liver-dominant metastatic colorectal cancer (mCRC) are largely unknown. **Patients and Methods:** This study was a retrospective analysis of 160 elderly (≥ 70 years) and 446 younger (< 70 years) consecutive patients from 11 US centers who received RE using ytrrium-90 (^{90}Y) resin microspheres (^{90}Y radioembolization [^{90}Y-RE]) between July 2002 and December 2011. A further analysis was conducted in 98 very elderly patients (≥ 75 years). Statistical analyses of safety, tolerability, and overall survival were conducted. **Results:** Mean ages (± standard deviation) in the younger (< 70 years), elderly (≥ 70 years), and very elderly (≥ 75 years) cohorts were 55.9 ± 9.4 years, 77.2 ± 4.8 years, and 80.2 ± 3.8 years, respectively. Overall survival was similar between elderly and younger patients: 9.3 months (95% confidence interval [CI], 8.0-12.1) and 9.7 months (95% CI, 9.0-11.4) (P = .335). There were no differences between cohorts for any grade adverse events (P = .433) or grade 3+ events (P = .482). Analysis of patients ≥ 75 years and < 75 years confirmed similar overall survival (median, 9.3 months vs. 9.6 months, respectively; P = .987) and grade 3+ events (P = .398) or any adverse event (P = .158) within 90 days of RE. **Conclusion:** For patients with unresectable liver-dominant mCRC who meet eligibility criteria for RE, ^{90}Y-RE microspheres appear to be effective and well-tolerated, regardless of age. Criteria for selecting patients for RE should not include age for exclusion from this potentially beneficial intervention.

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Introduction

Colorectal cancer (CRC) is the fourth most commonly diagnosed cancer in the United States.[1] Median age at diagnosis is 69 years, with 60% of new cases each year affecting patients older than 65 years (including 36% who are ≥ 75 years).[1] Studies of palliative and curative therapies purport similar outcomes in the elderly and young alike, demonstrating that chronologic age by itself is not a contraindication to treatment.[2] Nevertheless, population-based registries in the United States and Europe show that elderly patients (≥ 75 years) with CRC were 70% to 90% less likely to receive chemotherapy or radiotherapy than were younger patients,[3] despite evidence that many could have benefited from these treatments[4-9] and were less likely to receive surgical resection of the primary and/or secondary tumor.[9-13] With an underrepresentation of elderly patients in clinical trials,[14] only a few population-based studies have evaluated the true impact of treatment on the elderly.[9,15] To date, there is little guidance on the best treatment strategy for elderly patients with CRC taking into consideration both age-related[16,17] and treatment-related factors[18-20] to improve outcomes. Only 1 report to date has specifically studied age in patients receiving radioembolization (RE) for hepatic metastases from CRC.[21] In this retrospective study of 107 patients with CRC liver metastases treated at a single institution, 44 patients aged 70 years or older at the time of RE were compared with 63 patients younger than 70 years of age. Their conclusion was that toxicities and median survival were similar in both age groups after RE.[21]

The aim of this analysis from the **M**etastatic Colorectal Cancer Liver Metastases **O**utcomes After **R**adio**E**mbolization (MORE) study was to evaluate the effects of advancing age on the clinical outcomes after RE with yttrium-90 (^{90}Y)-labeled resin microspheres (^{90}Y radioembolization [^{90}Y-RE]). Data from the primary analyses in the overall cohort are published elsewhere.[22]

Patients and Methods

A retrospective study was conducted of consecutive patients who were referred to 11 US tertiary care centers for RE using ^{90}Y resin microspheres (SIR-Spheres; Sirtex, Sydney, Australia) between July 2002 and December 2011 (clinicaltrials.gov identifier: NCT01815879). All patients with a diagnosis of metastatic CRC (mCRC) who received at least 1 RE treatment and had at least 1 follow-up visit were included in the analyses. Institutional review board exemptions were granted before the collection of data at each site.

Centers were guided in the selection of patients, pretreatment workup, and dosimetry by the published consensus from the Radioembolization Brachytherapy Oncology Consortium (REBOC) and other earlier reviews.[23-25] ^{90}Y-RE was considered for those patients with advanced liver-dominant mCRC who were not suitable for (or who refused consent, or both) surgery, ablation, or systemic therapy or whose disease had progressed or who had become intolerant to at least 1 line of systemic therapy. Good candidates for ^{90}Y-RE included those with liver-only or liver-dominant mCRC, Eastern Cooperative Oncology Group (ECOG) performance status score of ≤ 2, and untreated life expectancy of ≥ 12 weeks. Patients with limited hepatic reserve, ascites, or other clinical signs of liver failure (total bilirubin level > 2.0 mg/dL in the absence of a reversible cause; serum albumin level of < 3.0 g/dL), or compromised bone marrow or pulmonary function were generally considered unsuitable for ^{90}Y-RE. During the pretreatment workup, patients were excluded from RE if there was evidence of any uncorrectable flow to nontarget sites (eg, gastrointestinal tract or other extrahepatic organs) observed on angiography or a technetium-99m macroaggregated albumin (^{99m}Tc-MAA) scan. Under exceptional circumstances and with informed consent, some patients were treated outside the criteria outlined based on the clinical judgment of the treating physicians.

The protocol for treatment within a single session or over multiple sessions (eg, using a sequential lobar approach for bilobar liver metastases) is reported elsewhere.[24] Most activity calculations for ^{90}Y-RE were planned using the body surface area methodology according to consensus guidelines.

Data Collection and Analysis

Safety data were collated on the day of the first ^{90}Y-RE procedure (day 0) and at all subsequent visits and included the results from all hematologic, liver function, and blood biochemistry tests and physical examinations. The nature and severity of all adverse events were graded using the Common Terminology Criteria for Adverse Events (CTCAE), version 3.0.[26] The highest grade occurring at any time between day 0 and day 90 after the procedure were reported. Survival was calculated from the day of the first ^{90}Y-RE procedure to the day of death or last follow-up.

Statistical Analysis

Statistical analyses were conducted using SAS, XP Pro, version 9.2, statistical analysis software (SAS Institute, Cary NC). Nonparametric estimates of survival were computed using the Kaplan-Meier product-limit method. The *P* values for continuous baseline variables were assessed by 1-way analysis of variance, for dichotomous variables by the Fisher exact test, and for nominal categorical variables by the χ^2 general association test. The CTCAE distribution between cohorts was compared using the Cochran-Mantel-Haenszel test.

Results

Patients

The baseline characteristics of 160 elderly (≥ 70 years) and 446 younger (< 70 years) patients are presented in Table 1, and the baseline characteristics of 98 very elderly patients (≥ 75 years) are presented in Supplemental Table 1 (see the online version). Mean ages (± standard deviation) in the younger (< 70 years), elderly (≥ 70 years), and very elderly (≥ 75 years) cohorts were 55.9 ± 9.4 years, 77.2 ± 4.8 years, and 80.2 ± 3.8 years, respectively. Regardless of age, patients eligible for ^{90}Y-RE had statistically similar baseline characteristics, although compared with the younger (< 70 years) patients, elderly (≥ 70 years) patients were more likely to have metachronous liver metastases ($P < .001$), to have had previous resection for a primary tumor ($P = .009$), to have received fewer lines of treatment ($P = .036$) or no previous chemotherapy ($P < .001$), and to have had a longer period between diagnosis and ^{90}Y-RE ($P = .011$). Notably, elderly patients were significantly less likely to have received previous treatment with oxaliplatin, irinotecan, and bevacizumab. Similar trends were also observed in the very elderly cohort (≥ 75 years) (see Supplemental Table 1 in the online

Table 1 Baseline Patient and Disease Characteristics, and Previous Procedures (N = 606)

Parameter	Category	Elderly Patients (≥70 years; n = 160) N (%)[a]	Younger Patients (<70 years; n = 446) N (%)[a]	*P* Value Across Cohorts
Sex, N (%)	Female/male	59 (36.9)/101 (63.1)	174 (39.0)/272 (61.0)	.705
Age, years	Mean ± SD (range)	77.2 ± (70.1-91.9)	55.9 ± (20.8-69.9)	<.001
	≥75 years	98 (61.3%)	NA	
Race, N (%)[b]	White or Caucasian	101 (63.1)	297 (66.6)	.429[c]
	Black or African American	11 (6.9%)	56 (12.6)	
	Hispanic or Latino	3 (1.9)	14 (3.1)	
	Asian	4 (2.5)	8 (1.8)	
	Other	5 (3.1)	13 (2.9)	
	Unknown	36	58	
ECOG Performance Status, N (%)[d]	0	41 (57.7)	127 (68.3)	.112[e]
	1	24 (33.8)	48 (25.8)	
	2	5 (7.0)	9 (4.8)	
	3	1 (1.4)	2 (1.1)	
	Unknown	89	260	
Site of Primary Tumor, N (%)[f]	Colon	135 (84.9)	308 (69.2)	.055[g]
	Rectum	21 (13.2)	112 (25.2)	
	Colorectal	3 (1.9)	25 (5.6)	
Primary Tumor in Situ N (%)[h]		11 (7.1)	67 (15.1)	.009
Metastases (%)[i,j]	Metachronous	64 (43.0)	109 (26.0)	<.001
	Synchronous	85 (57.0)	311 (74.0)	
Extrahepatic Metastases, N (%)		55 (34.4)	158 (35.4)	.847
Ascites, N (%) [k]	Yes	6 (3.9)	22 (5.0)	.555
Previous Liver-Directed Procedures, N (%)	Surgery or ablation, or both	47 (29.4)	121 (27.1)	.607
	Vascular/percutaneous	7 (4.4)	30 (6.7)	.340
	Upper abdominal radiation therapy	3 (1.9)	4 (0.9)	.388
Previous lines Of Systemic Chemotherapy for mCRC, N (%)	^{90}Y-RE first line	21 (13.6)	14 (3.3)	<.001
	^{90}Y-RE second line	50 (32.5)	156 (36.4)	.058[l]
	^{90}Y-RE third line	46 (29.9)	138 (32.2)	
	^{90}Y-RE fourth line plus	37 (24.0)	121 (28.2)	
	Unknown	6	17	
Previous Chemotherapeutic Agents, N (%)	Fluoropyrimidine	133 (83.1)	402 (90.1)	.022
	Oxaliplatin	107 (66.9)	350 (78.5)	.005
	Irinotecan	63 (39.4)	233 (52.2)	.006
	Bevacizumab	90 (56.3)	319 (71.5)	<.001
	EGFR inhibitor	42 (26.3)	124 (27.8)	.757
Time from mCRC Diagnosis to ^{90}Y-RE, months[m]	Median (range)	19.2 (0.4-90.6)	15.7 (0.6-96.3)	.295
Tumor-to-Treated Liver Volume (first session), N (%)[n]	<25	95 (66.4)	293 (70.6)	.709
	25-50	42 (29.4)	106 (25.5)	
	>50	6 (4.2)	16 (3.9)	
Albumin, g/dL[o]	Median (IQR)	3.6 (0.8)	3.7 (0.7)	.112
	CTCAE grade ≥1, N (%)	61 (38.9)	138 (31.8)	.116
Total Bilirubin, mg/dL[p]	Median (IQR)	0.7 (0.4)	0.6 (0.4)	.863
	CTCAE grade ≥1, N (%)	7 (4.5)	30 (6.9)	.339
Alkaline Phosphatase, U/L[k]	Median (IQR)	149.5 (148.5)	144.5 (138.0)	.787

Table 1 Continued

Parameter	Category	Elderly Patients (≥70 years; n = 160) N (%)[a]	Younger Patients (<70 years; n = 446) N (%)[a]	*P* Value Across Cohorts
	CTCAE grade ≥1, N (%)	95 (60.9)	256 (58.7)	.704
Creatinine, mg/dL[q]	Median (IQR)	1.0 (0.4)	0.8 (0.3)	<.001
	CTCAE grade ≥1, N (%)	16 (10.1)	10 (2.3)	<.001
Hemoglobin, g/dL[r]	Median (IQR)	12.2 (2.5)	12.5 (2.5)	.150
	CTCAE grade ≥1, N (%)	73 (46.2)	165 (37.8)	.072
Neutrophils, $\times 10^9$/L[s]	Median (IQR)	6.9 (2.9)	6.4 (3.2)	.184
	CTCAE grade ≥1, N (%)	4 (2.5)	37 (8.5)	.010
	Unknown	133	346	

Abbreviations: ECOG = Eastern Cooperative Oncology Group; EGFR = endothelial growth factor receptor; IQR = interquartile range; mCRC = metastatic colorectal carcinoma; SD = standard deviation.
[a]Calculated as a proportion of patients with known baseline data.
[b]Missing patient baseline data on 94 patients.
[c]*P* value: comparison of white (Caucasian) versus other.
[d]Missing patient baseline data on 349 patients.
[e]*P* value: comparison of ECOG performance status 0-1 versus 2+.
[f]Missing patient baseline data on 2 patients.
[g]*P* value: comparison of colon versus rectum.
[h]Missing patient baseline data on 6 patients.
[i]Missing patient baseline data on 37 patients.
[j]Synchronous defined as the identification of metastases within 4 months (120 days) of the diagnosis of the primary tumor.
[k]Missing patient baseline data on 14 patients.
[l]*P* value: continuous variable across all lines of chemotherapy.
[m]Missing patient baseline data on 29 patients.
[n]Missing patient baseline data on 48 patients.
[o]Missing patient baseline data on 15 patients.
[p]Missing patient baseline data on 13 patients.
[q]Missing patient baseline data on 11 patients.
[r]Missing patient baseline data on 12 patients.
[s]Missing patient baseline data on 479 patients.

version). A greater proportion of elderly patients was also affected by changes in kidney function at baseline (defined as CTCAE grade 1+ creatinine toxicity), although fewer had grade 1+ neutropenia (2.5% vs. 8.5%; $P < .001$). All patients eligible for ^{90}Y-RE, regardless of age, had similar liver function test findings at baseline.

Treatment

The treatment characteristics for ^{90}Y-RE by age are presented in Table 2 for patients ≥ 70 years versus those < 70 years and in Supplemental Table 2 (see the online version) for patients ≥ 75 years versus those < 75 years. Overall, 97% to 98% of patients were discharged from the hospital within 24 hours of the procedure in all age groups. Age was not a factor in determining the treatment approach for ^{90}Y-RE, but elderly patients were less likely to receive more than 1 ^{90}Y-RE procedure ($P = .007$), and a lower volume of liver was treated ($P < .001$) (Table 2). The radioactivity delivered during the first ^{90}Y-RE procedure was also slightly lower in the elderly (≥ 70 years) patients compared with the younger patients: 1.09 GBq (range, 0.110-2.04) versus 1.19 GBq (range, 0.130-2.29) ($P = .011$), although the median tumor-to−treated liver involvement was not statistically different between the cohorts.

Safety and Tolerability

Table 3 reports the findings from the safety analyses within the 90 days after the first ^{90}Y-RE procedure in elderly (≥ 70 years) patients, and these findings for very elderly (≥ 75 years) patients are reported in Supplemental Table 3 (see the online version). RE appeared to be equally well tolerated in the elderly (≥ 70 years) and younger patients, with no statistically significant differences in reporting of events by age for any grade ($P = .433$) or grade 3+ events ($P = .615$), although gastrointestinal events (any grade) were less likely to be reported in the elderly patients than in the younger patients (Table 3). Common (≥ 1%) grade 3+ events reported in the elderly (≥ 70 years) and the younger patients were abdominal pain (3.1% vs. 6.1%), gastritis or duodenitis (1.3% vs. 0.2%), nausea (0.6% vs. 1.3%), vomiting (1.3% vs. 1.3%), fatigue (5.6% vs. 4.5%), ascites (1.3% vs. 2.0%), hyperbilirubinemia (3.8% vs. 2.7%), and RE-induced liver disease (REILD) (1.3% vs. 0.2%), respectively. Similar findings for grade 3+ events were also observed in the analyses of the very elderly (≥ 75 years), with the exception of grade 3+ abdominal pain, which was less likely to be reported in the very elderly (1.0% vs. 6.1%; $P = .029$).

The most common event overall was mild to moderate fatigue, which tended to be more frequent in the elderly patients (≥ 70 years) than in the younger patients (41.3% vs. 34.5%), but between-group differences were not statistically significant for the reporting of this event for all grades ($P = .135$) or severe events ($P = .838$). Overall, the reporting of liver-function−related adverse events was low and not statistically significantly different compared with the younger cohorts in the analyses of either the elderly or the very elderly.

All-cause cumulative mortality did not differ significantly between younger patients (< 70 years) and elderly patients (≥ 70 years) on day 30 (3 [1.9%] vs. 9 [2.0%]; $P = 1.00$), day 60 (10 [6.3%] vs. 27 [6.1%]; $P = 1.00$), or day 90 after the procedure (29 [18.1%] vs. 56 [12.6%]; $P = .086$) nor was there a significant difference in the very elderly (≥ 75 years vs. < 75 years) on day 30

Table 2 Treatment Characteristics

Parameter	Category	Elderly Patients (≥70 years; n = 160) N (%)	Younger Patients (<70 years; n = 446) N (%)	*P* Value Across Cohorts
Target Treatment Approach (%)[a]	Whole-liver, single-session	45 (28.1)	134 (30.0)	.343
	Whole-liver, sequential lobar (<10 wk[b])	45 (28.1)	144 (32.3)	
	Whole-liver, sequential lobar (≥10 wk[b])	4 (2.5)	26 (5.8)	
	Right lobe ± segmental	49 (30.6)	119 (26.7)	
	Left lobe ± segmental	12 (7.5)	21 (16.8)	
	Segmental	3 (1.9)	2 (.4)	
First Session ^{90}Y Activity Delivered, GBq; median (range)		1.09 (0.1-2.0)	1.19 (0.1-2.3)	.011
Total ^{90}Y Activity Delivered, GBq; median (range)		1.24 (0.11-3.13)	1.53 (0.13-5.51)	<.001
Number of ^{90}Y-RE Sessions, N (%)	1	94 (58.8)	207 (46.4)	.007
	2	58 (36.3)	206 (46.2)	
	3	6 (3.8)	23 (5.2)	
	4	2 (1.3)	8 (1.8)	
	5	0	2 (.4)	
Lung Shunt (first session), %, median (range) (%)[c]		5.2 (0.5-45.0)	4.8 (0.0-31.0)	.215
Embolization of Nontarget Arteries (first session); N (%)[d]		124 (78.0)	375 (84.1)	.089
Hospital Stay Duration <24 h (first session); N (%)[e]		155 (97.5)	435 (98.0)	.752
Total Liver Volume (first session), mL; median (range)[f]		1541 (664-3118)	1842 (842-5844)	<.001
Treated Liver Volume (first session), mL; median (range)[g]		1247 (226-3118)	1486 (246-4772)	<.001
Total Tumor Volume (first session), mL; median (range)[h]		124 (4.0-1764)	157 (2.8-3329)	.268
Tumor-to—Treated Liver Ratio (first session session), %; median (range)[i]		15 (0.7-100)	15 (0.1-100)	.863
Follow-Up, months; median (range)		7.9 (0.6-48.6)	8.8 (0.1-77.7)	.341

Abbreviation: ^{90}Y-RE = yttrium-90 radioembolization.
[a]Missing patient baseline data on 1 patient.
[b]Denotes the interval between first and second treatments in patients receiving sequential lobar ^{90}Y-RE.
[c]Missing patient baseline data on 10 patients.
[d]Missing patient baseline data on 1 patient.
[e]Missing patient baseline data on 3 patients.
[f]Missing patient baseline data on 206 patients.
[g]Missing patient baseline data on 281 patients.
[h]Missing patient baseline data on 274 patients.
[i]Missing patient baseline data on 48 patients.

(3 [3.1%] vs. 9 [1.8%]; $P = .422$), day 60 (8 [8.2%] vs. 29 [5.7%]; $P = .357$), or day 90 (18 [18.4%] vs. 67 [13.2%]; $P = .203$).

Survival

Kaplan-Meier analyses found that survival differed little between elderly and younger patients (≥ 70 years vs. < 70 years: 9.3 months; [95% confidence interval {CI}, 8.0-12.1] vs. 9.7 months [95% CI, 9.0-11.4]; $P = .335$) and very elderly patients (≥ 75 years vs. < 75 years: 9.3 months [95% CI, 7.4-12.1] vs. 9.6 months [95% CI, 9.0-11.2]; $P = .987$) (Table 4; Figure 1; also see Supplemental Table 4 in the online version). For the very small group of patients (n = 35) who had received no previous chemotherapy, median survival differed significantly in patients ≥ 70 years (11.9 months) versus patients < 70 years (25.2 months). Further analysis revealed a multitude of reasons for recommending ^{90}Y-RE as a first-line therapy in this elderly cohort (including significant

Table 3 Common (≥ 1%)[a] All-Cause Adverse Events by Severity (CTCAE V3) and Any Procedure-Related Event Within Days 0-90 From First ^{90}Y-RE Procedure

System Organ, Class	Elderly Patients (≥70 years; n = 160) N (%)			Younger Patients (<70 years; n = 446) N (%)			*P* Value for All Grades[b]	*P* Value for Grade ≥3[c]
CTCAE Grade	Unknown	Grade 1-2	Grade ≥3	Unknown	Grade 1-2	Grade ≥3		
All (%)	0	77 (48.1)	27 (16.9)	4	217 (48.6)	84 (18.8)	.433	.482
Gastrointestinal (%)	0	57 (35.6)	10 (6.3)	3	191 (42.8)	43 (9.6)	.017	.152
Abdominal pain (%)	0	37 (23.2)	5 (3.1)	1 (0.2)	156 (35.0)	27 (6.1)	<.001	.157
Nausea (%)	1 (0.6)	31 (19.4)	1 (0.6)	3 (0.7)	122 (27.4)	6 (1.3)	.038	.736
Vomiting (%)	0	8 (5.0)	2 (1.3)	0	46 (10.3)	6 (1.3)	.067	1.000
GI Ulcer (%)	0	0	1 (0.6)	0	7 (1.6)	6 (1.3)	.128	.682
Abdominal Distention (%)	0	2 (1.3)	0	0	12 (2.7)	2 (0.4)	.260	1.000
Dyspepsia (%)	0	2 (1.3)	0	0	14 (3.1)	0	.260	NA
Gastritis (%)	0	1 (0.6)	1 (0.6)	0	2 (0.4)	1 (0.2)	.611	.459
Duodenitis (%)	0	0	1 (0.6)	0	0	0	.264	.264
Intestinal obstruction (%)	0	0	1 (0.6)	0	1 (0.2)	3 (0.7)	1.000	1.000
Constipation (%)	1 (0.6)	5 (3.1)	0	1 (0.2)	13 (2.9)	0	.797	NA
Diarrhea (%)	0	2 (1.3)	0	0	7 (1.6)	0	1.000	NA
Flatulence (%)	0	1 (0.6)	0	0	5 (1.1)	0	1.000	NA
Constitutional (%)	1	67 (41.4)	10 (6.3)	5	167 (37.4)	23 (5.2)	.308	.851
Fatigue (%)	0	66 (41.3)	9 (5.6)	3 (0.7)	154 (34.5)	20 (4.5)	.135	.838
Fever (%)	1 (0.6)	7 (4.4)	0	1 (0.2)	34 (7.6)	2 (0.4)	.219	1.000
Weight loss (%)	0	2 (1.3)	0	1 (0.2)	5 (1.1)	0	1.000	1.000
Peripheral edema (%)	0	0	0	1 (0.2)	1 (0.2)	2 (0.4)	.578	.570
Psychiatric (%)	0	11 (6.9)	1 (0.6)	3 (0.7)	29 (6.5)	4 (0.9)	1.000	.688
Anorexia nervosa (%)	0	11 (6.9)	1 (0.6)	3 (0.7)	28 (6.3)	4 (0.9)	1.000	.688
Hepatobiliary (%)	0	11 (6.9)	7 (4.4)	0	35 (7.8)	28 (6.3)	.417	.435
Hyperbilirubinemia (%)	0	8 (5.0)	6 (3.8)	0	29 (6.5)	12 (2.7)	1.000	.587
Ascites (%)	0	2 (1.3)	2 (1.3)	1 (0.2)	7 (1.6)	9 (2.0)	.615	.741
REILD (%)	0	2 (1.3)	2 (1.3)	5 (1.1)	0	1 (0.2)	.302	1.000
Cholecystitis (%)	0	1 (0.6)	0	0	3 (0.7)	1 (0.2)	1.000	1.000
Hepatic failure (%)	0	1 (0.6)	0	0	1 (0.2)	2 (0.4)	1.000	1.000
Musculoskeletal (%)	0	2 (1.3)	0	1 (0.2)	13 (2.9)	1 (0.2)	.263	1.000
Back pain (%)	0	1 (0.6)	0	0	4 (0.9)	0	1.000	NA

Table 3 Continued

System Organ, Class	Elderly Patients (≥70 years; n = 160) N (%)			Younger Patients (<70 years; n = 446) N (%)			*P* Value for All Grades[b]	*P* Value for Grade ≥3[c]
Vascular Disorders (%)	0	3 (1.9)	3 (1.9)	1 (0.2)	4 (0.9)	3 (0.7)	.215	.388
Respiratory (%)	1	3 (1.9)	1 (0.6)	1 (0.2)	14 (3.1)	1 (0.2)	1.000	.285
Influenza (%)	0	1 (0.6)	0	1 (0.2)	9 (2.0)	0	.304	1.000

Abbreviations: CTCAE V3 = Common Terminology Criteria for Adverse Events, version 3; GI = gastrointestinal; NA = not applicable; REILD = radioembolization-induced liver disease; ^{90}Y-RE = yttrium-90 radioembolization.
[a]At all time points; this table reports the highest grade of adverse event reported by each patient within each time interval.
[b]*P* value between cohort comparison of all grades.
[c]*P* value for between cohort comparison of grades ≥ 3.

comorbidities and secondary malignancies), which may have accounted for these survival differences.

Discussion

MORE is the largest study of RE of any tumor type, including mCRC, with > 600 patients who were treated between 2002 and 2011. Nevertheless, as with so many studies in the real-world setting as well as clinical trials with chemotherapy,[27,28] there tends to be an underrepresentation of elderly patients (median age 59 years at diagnosis in the MORE study) compared with those who are diagnosed with CRC each year who have a median age of 69 years (based on the Surveillance, Epidemiology and End Results [SEER] data 2006-2010)[1] (Figure 2). This probably reflects the lower referral rate of elderly patients for liver-directed therapy or the lower propensity of elderly patients to travel to specialized clinics because of factors such as frailty and declining cognitive function and malnutrition,[2,16,17] rather than the exclusion of elderly patients during the pretreatment workup for ^{90}Y-RE. It is notable that greater proportions of elderly patients than of younger patients (18.4% vs. 3.3%) were referred for liver-directed therapy and received ^{90}Y-RE having been considered ineligible for palliative chemotherapy.

It is of interest that the only other report related specifically to the age of patients with mCRC at the time of ^{90}Y-RE[21] details results very similar to those of the MORE study (Table 5). Period of treatment, eligibility criteria, toxicity assessment with CTCAE, version 3.0, imaging interval, and median radioactivity or ^{90}Y delivered are the same in this study and the Tohme et al study.[21] Neither study detected a statistical difference in any category regarding toxicity, response, and survival between patients aged < 70 years and patients > 70 years.

Even though the baseline tumor characteristics and liver function were similar in patients eligible for ^{90}Y-RE, a higher proportion of very elderly patients (> 75 years) compared with younger (< 75 years) patients had a reduced performance status (ECOG 1-2: 42.2% vs. 32.3%; $P = .068$). This finding may have been an underestimate of the actual performance status across the whole cohort because unfortunately performance status was not routinely assessed during clinical workup in nearly half of patients. Overall, elderly patients compared with younger patients were less likely to receive more than 1 ^{90}Y-RE procedure, and a lower volume of liver was treated with a lower median activity of ^{90}Y-RE. These data suggest that a more conservative treatment approach was adopted in the elderly, albeit without a significant detrimental effect on survival.

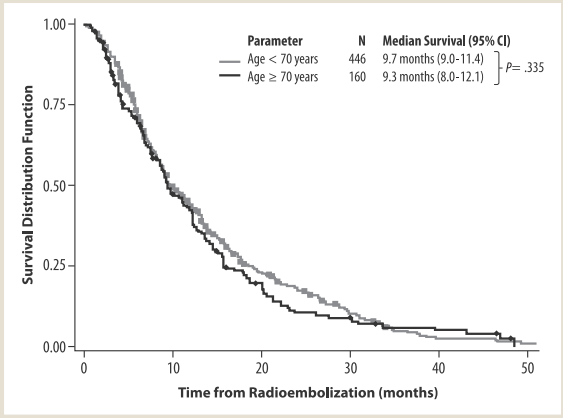
It is encouraging to note that a recently published review of cancer registry/Medicare data (over a similar period between 2000 and 2009) found that survival in advanced CRC is improving by 4% each year in the elderly after controlling for treatment and tumor location.[9] Notably, the registry found that modern chemotherapeutic agents (ie, oxaliplatin, irinotecan, and bevacizumab) are increasingly being adopted for the elderly, perhaps suggesting a shift in practice patterns[9]; although our study and other published analyses suggest that elderly patients were still significantly less likely to receive these agents than were younger patients.[4,19,29] Perhaps as a consequence, a significantly greater incidence of grade 1+ neutropenia was observed at baseline in younger patients than in elderly patients,[18,30] even in the relatively small number of patients evaluated for neutropenia in this study.

Table 4 Kaplan-Meier Analysis of Survival in All Patients and by Previous Lines of Chemotherapy

Characteristic	Category	Survival, months[a] Elderly Patients (≥70 years; n = 160)				Survival, months[a] Younger Patients (<70 years; n = 446)				*P* Value Across Cohorts
		N	Median	95% CI	*P* Value[b]	N	Median	95% CI	*P* Value[b]	
All		160	9.3	8.0-12.1	NA	446	9.7	9.0-11.4	NA	.335
Previous Lines of Chemotherapy	^{90}Y-RE first line	21	12.8	6.0-15.7	.146	14	25.4	7.1-36.5	<.001	.032
	^{90}Y-RE second line	50	11.6	8.5-15.1		156	13.2	10.5-16.3		.652
	^{90}Y-RE third line	46	9.1	6.8-12.1		138	9.0	7.8-11.3		.167
	^{90}Y-RE fourth line plus	37	6.5	3.8-9.3		121	8.3	6.4-9.5		.761

Abbreviations: CI = confidence interval; NA = not applicable; ^{90}Y-RE = yttrium-90 radioembolization.
[a]Median survival calculated by Kaplan-Meier analysis.
[b]*P* value for within-cohort comparison by previous lines of chemotherapy.

Figure 1 Kaplan-Meier Survival Curves of Patients With Metastatic Colorectal Cancer (mCRC) After Treatment With Ytrrium-90 Radioembolization (^{90}Y-RE) Stratified by Age



Overall, we found that ^{90}Y-RE was equally well tolerated in eligible elderly (≥ 70 years) and very elderly (≥ 75 years) and younger patients, without evidence of an increased risk of REILD or hepatic dysfunction in the elderly who were assessed up to 90 days after the procedure. The incidence of grade 3+ events after ^{90}Y-RE was low. Mild to moderate fatigue was slightly more prominent in the elderly than in the younger patients, although between-group differences were not statistically significant.

The period between diagnosis and ^{90}Y-RE was longer in the elderly ($P = .011$). Despite this, a greater proportion of very elderly and elderly patients than of younger patients received ^{90}Y-RE as

Figure 2 Percentage of Cases by Age at Diagnosis in the Metastatic Colorectal Cancer Liver Metastases Outcomes After Radioembolization (MORE) Study and the Surveillance, Epidemiology and End Results (SEER) (2006-2010) Database (Vertical Line Shows the Median Age at Diagnosis in Each Cohort)

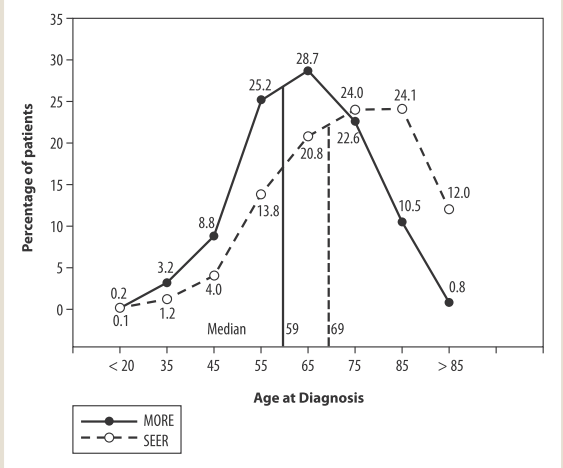


Table 5 Comparison of Current Study Parameters With Study by Tohme

	Tohme et al[21]	Current Study
No. of Patients	107	606
Age, years (no. patients)		
<70	63	446
>70	44	160
		(98 patients >75 years)
Time of Study	2002-2012	2002-2011
^{90}Y Activity Calculation	Modified partition method	Body surface area method
Eligibility	REBOC	REBOC
Treatment Approach	Lobar	43% whole liver
		43% lobar
Posttreatment	Overnight stay in hospital	99% discharged same day
Toxicity	CTCAE, version 3.0; d 1-90 after procedure	CTCAE, version 3.0; d 1 until death
Imaging Assessment	RECIST 1.1 up to 6 mo after ^{90}Y-RE	RECIST 1.0 and 1.1 at 3 mo after ^{90}Y-RE
Survival	From d of ^{90}Y-RE procedure	From d of ^{90}Y-RE procedure

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; REBOC = Radioembolization Brachytherapy Oncology Consortium; ^{90}Y-RE = ytrrium-90 radioembolization.

first-line treatment (18.4% and 13.6% vs. 3.3%, respectively), with fewer elderly patients receiving the procedure as second- or third-line therapy (57.1%, 62.4% vs. 68.6%, respectively). Radioembolization was considered in preference to systemic chemotherapy in up to a fifth of very elderly patients with mCRC, many of whom had refused further chemotherapy at the end of adjuvant treatment after resection of the primary tumor or had significant comorbidities and secondary malignancies. For this reason, median survival with first-line ^{90}Y-RE was lower in the elderly than in younger patients (12.8 months vs. 25.4 months), which is consistent with recent experience with capecitabine and oxaliplatin in elderly and frail patients (median survival, 11 months)[31] and in the UK MRC open-label FOCUS2 study of elderly patients $\geq$ 70 years (median age, 75 years; median survival, 10.2-12.4 months).[7] In the chemotherapy-refractory setting, however, overall survival was not statistically different in elderly and younger patients when RE was given either as second-line treatment (11.6 vs. 13.2 months) or third-line treatment (9.1 vs. 9.0 months).

Comparisons of the MORE study with prospective randomized controlled trials are hampered by differences in the selection criteria between these studies. For example, most randomized controlled trials in the elderly tend to select patients with a good performance status (ie, either an ECOG score of 0 or a KPS score of 80%-100%) and many only in the first-line setting.[5,32-35] For example, 69%-88% of elderly patients in studies using cetuximab had a good performance status[36,37] compared with only 58% of patients in the MORE study. Nevertheless, our experience with RE in the second-line setting and beyond in elderly patients compares favorably with the survival beyond progression of 10 to 12 months in the Bevacizumab Regimens: Investigation of Treatment Effects and Safety (BRiTE) study of bevacizumab-based first-line therapy,[33] but without the increased risk of significant toxicity associated with systemic chemotherapy in the elderly, who frequently require dose reductions.[5,18,38-42] With the risk of toxicities to chemotherapy amplified in frail patients[16] as well as beyond first-line therapy,[18] RE appears to be a particularly attractive alternative for the management of elderly patients with liver-dominant mCRC. The 90-day all cause mortality seen in this study is in keeping with that expected in patients who have progressed beyond fourth-line chemotherapy or who have been medically unable to receive multiagent chemotherapy beyond first-line regimens. The treatment intensity (activity delivered) was not significantly different between young and elderly patient cohorts. The percentage of patients receiving whole liver versus lobar treatments was also the same in each group. Very few (< 10) patients were reported to have received any additional systemic therapy beyond RE, which is not unusual given that they had already received multiple lines of therapy before RE.

Conclusion

For patients with unresectable liver-dominant mCRC who meet the eligibility criteria for RE, ^{90}Y-RE appears to be as effective and as well tolerated in elderly patients as in younger candidates. Because elderly patients receive less intense systemic therapy, liver tumor control may provide significant benefits in select patients.

Clinical Practice Points

- Patients with mCRC who are older than 65 years constitute at least 60% of new cases yearly, and 36% of these patients are 75 years or older. However, for a variety of reasons, patients > 70 years ("elderly") do not receive anticancer therapy that is as intensive as that given to younger patients with mCRC.
- Elderly patients are often ineligible for clinical studies in mCRC, and as such there is a knowledge gap in how to optimally care for them.
- The current question addressed in this report is the safety and efficacy of liver-directed radiation ^{90}Y-RE delivered intraarterially and permanently implanted into liver metastases in elderly patients.
- Only 1 other report appears in the current literature concerning elderly patients receiving this therapy, and it has a modest number of participants. It describes treatment eligibility and approach to delivery of radiation similar to the current report.
- However, the current study greatly expands the level of detailed information on treatment and outcome, and includes 4 times as many patients as the previous report. In addition, there are new data provided for 95 patients who were older than 75 years when treated.
- Overall, the complimentary and new data reported will enable confidence in offering liver irradiation to patients older than 70 years. These patients are underserved currently, and thus this approach is likely to directly benefit both the quality and quantity of life in elderly patients.

Authors Contributions

Conception and design: A.S.K., D.C., C.N., S.S.

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Supplemental Data

Supplemental figure and tables accompanying this article can be found in the online version at http://dx.doi.org/10.1016/j.clcc.2015.09.001.

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Supplemental Table 1 Baseline Patient and Disease Characteristics and Previous Procedures in the Very Elderly Compared With Younger Patients

Parameter	Category	Very Elderly Patients (≥75 years; n = 98) N (%)[a]	Younger Patients (<75 years; n = 508) N (%)[a]	*P* Value Across Cohorts
Sex, N (%)	Female/male	33 (33.7)/65 (66.3)	200 (39.4)/308 (60.6)	.309
Age, years	Mean ± SD	80.2 ± 3.8	57.9 ± 10.4	<.001
	(range)	(75.0-91.9)	(20.8-74.9)	
Race, N (%)[b]	White or Caucasian	59 (79.7)	339 (77.4)	.213[c]
	Black or African American	8 (10.8)	59 (13.5)	
	Hispanic or Latino	2 (2.7)	15 (3.4)	
	Asian	2 (2.7)	10 (2.3)	
	Other	3 (4.1)	15 (3.4)	
	Unknown	24	70	
ECOG Performance Status, N (%)[d]	0	25 (54.3)	143 (67.8)	.068[e]
	1	16 (34.8)	56 (26.5)	
	2	4 (8.7)	10 (4.7)	
	3	1 (2.2)	2 (0.9)	
	Unknown	52	297	
Site of Primary Tumor, N (%)[f]	Colon	82 (84.5)	361 (71.2)	.189[g]
	Rectum	2 (2.1)	26 (5.1)	
	Colorectal	13 (13.4)	120 (23.7)	
Primary Tumor in Situ N (%)[h]		5 (5.3)	73 (14.5)	.012
Metastases, N (%)[i,j]	Metachronous	43 (48.3)	130 (27.1)	<.001
	Synchronous	46 (51.7)	350 (72.9)	
Extrahepatic Metastases, N (%)		31 (31.6)	182 (35.8)	0.488
Ascites, N (%)[k]	Yes	4 (4.2)	24 (4.8)	.792
Previous Liver-Directed Procedures, N (%)	Surgery and/or ablation	27 (27.6)	141 (27.8)	1.000
	Vascular/percutaneous	4 (4.1)	33 (6.5)	.491
	Upper abdominal radiation	1 (1.0)	6 (1.2)	1.000
Previous Lines of Systemic Chemotherapy for mCRC, N (%)	RE first line	18 (18.9)	17 (3.5)	<.005
	RE second line	30 (31.6)	176 (36.1)	.004[l]
	RE third line	26 (27.4)	158 (32.4)	
	RE fourth line +	21 (22.1)	137 (28.0)	
	Unknown	3	20	
Previous Chemotherapy Agents, N (%)	Fluoropyrimidine	81(82.7)	454 (89.4)	.084
	Oxaliplatin	60 (61.2)	397 (78.1)	<.001
	Irinotecan	33 (33.7)	263 (51.8)	.001
	Bevacizumab	51(52.0)	358 (70.5)	<.001
	EGFR inhibitor	22 (22.4)	144 (28.3)	.266
Time From mCRC Identification to RE, mo[m]	Median (range)	17.0 (0.4-78.0)	16.1 (0.6-96.3)	.042
Tumor-to-Target, N (%)	<25	62 (71.3)	326 (69.2)	.589
Liver (first session), N (%)[n]	25-50	22 (25.3)	126 (26.8)	
	>50	3 (3.4)	19 (4.0)	
Albumin, g/dL[k]	Median (IQR)	3.6 (0.7)	3.7 (0.8)	.472
	CTCAE grade ≥1, N (%)	36 (37.9)	163 (32.9)	.345
Total Bilirubin, mg/dL[o]	Median (IQR)	0.7 (0.4)	0.6 (0.4)	.908

Supplemental Table 1 Continued

Parameter	Category	Very Elderly Patients (≥75 years; n = 98) N (%)[a]	Younger Patients (<75 years; n = 508) N (%)[a]	*P* Value Across Cohorts
	CTCAE grade ≥1, N (%)	3 (3.2)	34 (6.8)	.246
Alkaline phosphatase, U/L[p]	Median (IQR)	148.5 (127.0)	145.0 (144.0)	.204
	CTCAE grade ≥1, N (%)	55 (58.5)	296 (59.4)	.909
Creatinine, mg/dL[q]	Median (IQR)	1.0 (0.3)	0.8 (0.3)	<.001
	CTCAE grade ≥1, N (%)	10 (10.4)	16 (3.2)	.004
Hemoglobin, g/dL[r]	Median (IQR)	12.2 (2.2)	12.5 (2.6)	.600
	CTCAE grade ≥1, N (%)	44 (45.4)	194 (39.0)	.259
Neutrophils, $\times 10^9$/L[s]	Median (IQR)	4.4 (2.1)	4.1 (2.2)	.404
	CTCAE grade ≥1, N (%)	1 (7.7)	7 (6.1)	.589

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; ECOG = Eastern Cooperative Oncology Group; EGFR = endothelial growth factor receptor; IQR = interquartile range; mCRC = metastatic colorectal carcinoma; RE = radioembolization; SD = standard deviation.
[a]Calculated as a proportion of patients with known baseline data.
[b]Missing patient baseline data on 94 patients.
[c]*P* value: comparison of Caucasian versus other.
[d]Missing patient baseline data on 349 patients.
[e]*P* value: comparison of ECOG performance status 0-1 versus 2+.
[f]Missing patient baseline data on 2 patients.
[g]*P* value: comparison of colon versus rectum.
[h]Missing patient baseline data on 6 patients.
[i]Missing patient baseline data on 37 patients.
[j]Synchronous defined as the identification of metastases within 4 months (120 days) of finding the primary tumor.
[k]Missing patient baseline data on 15 patients.
[l]*P* value: continuous variable across all lines of chemotherapy.
[m]Missing patient baseline data on 29 patients.
[n]Missing patient baseline data on 48 patients.
[o]Missing patient baseline data on 13 patients.
[p]Missing patient baseline data on 14 patients.
[q]Missing patient baseline data on 11 patients.
[r]Missing patient baseline data on 12 patients.
[s]Missing patient baseline data on 479 patients.

Supplemental Table 2 Treatment Characteristics in Very Elderly Compared With Younger Patients

Parameter	Category	Very Elderly Patients (≥75 years; n = 98) N (%)	Younger Patients (<75 years; n = 508) N (%)	*P* Value Across Cohorts
Target Treatment Approach, N (%)	Whole liver, single session	22 (22.4)	109 (21.5)	.343
	Whole liver, sequential lobar (<10 wk[a])	27 (27.6)	190 (37.4)	
	Whole liver, sequential lobar (≥10 wk[a])	8 (8.2)	47 (9.2)	
	Right lobe ± segmental	31 (31.6)	134 (26.4)	
	Left lobe ± segmental	8 (8.2)	25 (4.9)	
	Segmental	2 (2.0)	3 (0.6)	
First Session ^{90}Y Activity Delivered, GBq; median (range)		1.02 (0.11-2.04)	1.19 (0.13-2.29)	.011
Total ^{90}Y Activity Delivered, GBq; median (range)		1.22 (0.11-3.12)	1.49 (0.13-5.51)	<.001
No. of ^{90}Y-RE sessions, N (%)	1	61 (62.2)	240 (47.2)	.007
	2	33 (33.7)	231 (45.5)	
	3	4 (4.1)	25 (4.9)	
	4	0	10 (2.0)	
	5	0	2 (0.4)	
Lung Shunt (first session), %, median (range)[b]		5.0 (0.5-45.0)	4.8 (0.0-31.0)	.290
Embolization of Nontarget Arteries (first session), N (%)[c]		70 (72.2)	429 (84.4)	.005
Hospital stay duration <24 h (first session), N (%)[d]		94 (96.9)	496 (98.0)	.449
Total Liver Volume (first session), mL, median (range)[e]		1481 (664-2635)	1825 (842-5844)	<.001
Treated Liver Volume (first session), mL, median (range)[f]		1179 (226-2083)	1451 (246-4772)	<.001
Total Tumor Volume (first session), mL, median (range)[g]		76.4 (4.0-1080)	164 (2.8-3329)	.039
Tumor-to—Treated Liver Ratio (first session), %, median (range)[h]		10 (0.9-71)	15 (0.1-100)	.589
Follow-Up, mo, median (range)		7.4 (0.6-48.6)	8.9 (0.1-77.7)	.597

P value for continuous variables by 1-way analysis of variance, *P* values for dichotomous variables by the Fisher exact test, nominal categorical variables by χ^2 general association test, and *P* value for ordinal variables by Wilcoxon rank sum test.
Abbreviation: ^{90}Y = yttrium 90; RE = radioembolization.
[a]Denotes the interval between first and second treatments in patients receiving sequential lobar ^{90}Y-RE.
[b]Missing patient baseline data on 10 patients.
[c]Missing patient baseline data on 1 patient.
[d]Missing patient baseline data on 3 patients.
[e]Missing patient baseline data on 206 patients.
[f]Missing patient baseline data on 281 patients.
[g]Missing patient baseline data on 274 patients.
[h]Missing patient baseline data on 48 patients.

Supplemental Table 3 Common (≥ 1%)[a] All-Causality Adverse Events by Severity (CTCAE, version 3) and Any Procedure-Related Event Within Days 0-90 from First ^{90}Y-RE Procedure

System Organ, Class	Very Elderly Patients (≥75 years; n = 98) N (%)			Younger Patients (<75 years; n = 508) N (%)			*P* Value for All Grades[b]	*P* Value for Grade ≥3[c]
CTCAE Grade	Unknown	Grade 1-2	Grade ≥3	Unknown	Grade 1-2	Grade ≥3		
All, N (%)	0	45 (45.9)	15 (15.3)	4 (0.8)	249 (49.0)	96 (18.9)	.158	.398
Gastrointestinal, N (%)	0	35 (35.7)	4 (4.1)	3 (0.6)	213 (41.9)	49 (9.6)	.027	.057
Abdominal pain, N (%)	0	23 (23.5)	1 (1.0)	1 (0.2)	170 (33.5)	31 (6.1)	.004	.029
Nausea, N (%)	1 (1.0)	20 (20.4)	0	3 (0.6)	133 (26.2)	7 (1.4)	.214	1.000
Vomiting, N (%)	0	5 (5.1)	1 (1.0)	0	49 (9.6)	7 (1.4)	.201	1.000
Ulcer, N (%)	0	0	0	0	7 (1.4)	7 (1.4)	.142	.605
Abdominal distention, N (%)	0	1 (1.0)	0	0	13 (2.6)	2 (0.4)	.490	1.000
Dyspepsia, N (%)	0	0	0	0	16 (3.2)	0	.088	NA
Gastritis, N (%)	0	1 (1.0)	1 (1.0)	0	2 (0.4)	1 (0.2)	.186	.298
Duodenitis, N (%)	0	0	1 (1.0)	0	0	0	.162	.162
Intestinal obstruction, N (%)	0	0	1 (1.0)	0	1 (0.2)	3 (0.6)	.587	.507
Constipation, N (%)	1 (1.0)	4 (4.0)	0	1 (0.2)	14 (2.8)	0	.348	.298
Diarrhea, N (%)	0	2 (2.0)	0	0	7 (1.4)	0	.644	NA
Flatulence, N (%)	0	0	0	0	6 (1.2)	0	.596	NA
Constitutional	1 (1.0)	39 (39.8)	4 (4.1)	5 (1.0)	195 (38.4)	29 (5.7)	1.000	.659
Fatigue, N (%)	0	39 (39.8)	4 (4.1)	3 (0.6)	181 (35.6)	25 (4.9)	.655	.805
Fever, N (%)	1 (1.0)	5 (5.1)	0	1 (0.2)	36 (7.1)	2 (0.4)	.680	.507
Weight loss, N (%)	0	2 (2.0)	0	1 (0.2)	5 (1.0)	0	.622	1.000
Peripheral edema, N (%)	0	0	0	1 (0.2)	1 (0.2)	2 (0.4)	1.000	1.000
Psychiatric	0	7 (7.1)	0	3 (0.6)	33 (6.5)	5 (1.0)	1.000	.366
Anorexia nervosa, N (%)	0	7 (7.1)	0	0	32 (6.3)	5 (1.0)	1.000	.366
Hepatobiliary, N (%)	0	6 (6.1)	3 (3.1)	0	40 (7.9)	32 (6.3)	.255	.341
Hyperbilirubinemia, N (%)	0	4 (4.0)	2 (2.0)	0	33 (6.5)	16 (3.1)	.338	.751
Ascites, N (%)	0	0	1 (1.0)	1 (0.2)	9 (1.8)	10 (2.0)	.226	.701
REILD, N (%)	0	2 (2.0)	1 (1.0)	5 (1.0)	0	2 (0.4)	.210	1.000
Cholecystitis, N (%)	0	1 (1.0)	0	0	3 (0.6)	1 (0.2)	.587	1.000
Hepatic failure, N (%)	0	0	0	0	2 (0.4)	2 (0.4)	1.000	1.000
Musculoskeletal, N (%)	0	2 (2.0)	0	1 (0.2)	13 (2.6)	1 (0.2)	1.000	1.000
Back pain, N (%)	0	1 (1.0)	0	0	4 (0.8)	0	.587	NA
Cardiac disorders, N (%)	0	0	2 (2.0)	0	1 (0.2)	0	.070	.026

Supplemental Table 3 Continued

System Organ, Class	Very Elderly Patients (≥75 years; n = 98) N (%)			Younger Patients (<75 years; n = 508) N (%)			*P* Value for All Grades[b]	*P* Value for Grade ≥3[c]
Vascular Disorders, N (%)	0	2 (2.0)	2 (2.0)	1 (0.2)	5 (1.0)	4 (0.8)	.259	.316
Respiratory, N (%)	1 (1.0)	1 (1.0)	1 (1.0)	1 (0.2)	16 (3.1)	1 (0.2)	1.000	.125
Influenza, N (%)	0	0	0	1 (0.2)	10 (2.0)	0	.227	1.000

This table reports the highest grade of adverse event reported by each patient within each time interval.
Abbreviations: NA = not applicable; REILD = radioembolization-induced liver disease.
[a]At all time points.
[b]*P* value across all grades.
[c]*P* value for grades ≥ 3.

Supplemental Table 4 Kaplan-Meier Analysis of Survival in All Patients and by Previous Lines of Chemotherapy

Characteristic	Category	Survival, months[a] Very Elderly Patients (≥75 years; n = 98)				Survival, months[a] Younger Patients (<75 years; n = 508)				*P* Value Across Cohorts[c]
		N	Median	(95% CI)	*P* Value[b]	N	Median	(95% CI)	*P* Value[b]	
All		98	9.3	(7.4-12.1)	NA	508	9.6	(9.0-11.2)	NA	.987
Previous Lines of Chemotherapy	RE first line	18	11.9	(4.0-15.6)	.316	17	25.2	(9.3-36.5)	<.001	.041
	RE second line	30	12.1	(7.4-20.2)		176	13.0	(10.5-14.6)		.733
	RE third line	26	8.7	(5.0-12.1)		158	9.0	(7.8-10.4)		.360
	RE fourth line +	21	6.6	(4.4-9.3)		137	8.2	(6.4-9.4)		.963

Abbreviations: CI = confidence interval; NA = not applicable; RE = radioembolization.
[a]Median survival calculated by Kaplan-Meier analysis.
[b]*P* value for within-cohort comparison by previous lines of chemotherapy.
[c]*P* value for across-cohort comparison.

Supplemental Figure 1 Kaplan-Meier Survival Curves of Patients With Metastatic Colorectal Cancer (mCRC) After Radioembolization (RE) Using Yttrium-90 (^{90}Y) Resin Microspheres, Stratified by Age (< 75 years vs. ≥ 75 years)